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UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Case No. 13-md-2452-AJB-MDD

DEFENDANTS' REPLY MEMORANDUM IN SUPPORT OF THEIR MOTION FOR SUMMARY JUDGMENT BASED ON PREEMPTION

Date: July 1, 2014
Time: 9:30 a.m.
Courtroom: 3B
Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

Conceding they do not have "facts essential to justify [their] opposition" to a preemption defense, plaintiffs speculate that with more time and more discovery, some might turn up.[1] But the relevant facts are a matter of public record: (1) FDA conducted a year-long investigation relating to a possible risk of pancreatic cancer, then took the unprecedented step of publishing in the nation's most prominent medical journal an official statement that the current labeling is adequate; (2) FDA rejected a Public Citizen Petition to remove Victoza from the market, finding "no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support *any* changes to the current approved labeling";[2] and (3) FDA twice in 2014 approved incretin-based therapies without requiring a pancreatic-cancer warning. These facts are clear and indisputable evidence that FDA would not approve a pancreatic-cancer warning.

A. The Facts Constituting "Clear Evidence" Are Undisputed.

Prompted by the same scientific and media reports that launched plaintiffs' complaints—reports that incretin-based therapies might increase the risk of pancreatic cancer—FDA in conjunction with the European Medicines Agency (EMA) launched "comprehensive evaluations" of the issue.

There is no dispute what FDA did. As FDA reported in the *New England Journal of Medicine* (*NEJM*), its "comprehensive evaluations" entailed: (1) "re-evaluat[ing] 250 toxicology studies"; (2) "requir[ing] sponsors of marketed incretin-based drugs to conduct 3-month pancreatic toxicity studies in a rodent model of diabetes"; (3) subjecting 120 pancreatic histopathology slides "to independent and blinded examination by three FDA pathologists"; (4) "perform[ing] its own

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[1] Plaintiffs' Mem. of P. & A. ("Opp.") at 1 (brackets in original).

[2] Public Citizen Letter ("PCL") at 26, 37 (emphasis added).

pancreatic toxicology studies with exenatide"; (5) reviewing clinical safety databases including "data from more than 200 trials, involving approximately 41,000 participants"; (6) analyzing pancreatic cancer data from two cardio-outcome trials (20,000 patients); and (7) "independently review[ing] a number of observational studies." Egan, et al., *Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment*, N. Engl. J. Med. 370:9 (Feb. 27, 2014) ("FDA/EMA Assessment").

There is no dispute what FDA concluded. FDA determined in February 2014 that "the current knowledge [concerning a causal association between incretin-based therapies and pancreatitis or pancreatic cancer] is *adequately reflected in the product information and labeling*." It reached this conclusion because the assertions suggesting a causal association "expressed recently in the scientific literature and in the media are *inconsistent with the current data*." *Id*. (emphasis added). This official statement—only three months old—that the current labeling is adequate and that the scientific data does not warrant a labeling change is alone "clear evidence" that FDA would not approve a pancreatic-cancer warning, however worded.

This official statement is just one of four official actions—all in 2014—reflecting FDA's judgment that a pancreatic-cancer warning is not warranted at this time. Also in February, FDA approved an extended-release formulation of exenatide (Bydureon) without requiring a pancreatic-cancer warning; in March, FDA rejected a Public Citizen Petition to withdraw Victoza from the market, finding "no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support *any* changes to the current approved labeling," PCL at 26, 37; and, in April, FDA approved a new incretin-based medication, Tanzeum, without requiring a pancreatic-cancer warning.[3]

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[3] What was not true at the time of the events in *Levine*, but has been true since 2007, is that FDA can require a labeling change if it "becomes aware of new safety information that the Secretary believes should be included in the labeling of the

Thus, plaintiffs miss the mark when they assert that "Defendants ask this Court to speculate about what the FDA *might* do in response to a hypothetical pancreatic cancer warning." Opp. at 3. To the contrary, defendants ask the Court to credit what FDA has *done* (conduct a comprehensive evaluation of the pancreatic safety of incretin-based therapies) and what FDA has *concluded* four times in the last four months (a pancreatic-cancer warning is not warranted because a causal association with pancreatic cancer is "inconsistent with the current data"). These facts are not open to dispute; they are a matter of public record. And they meet the "clear evidence" standard established in *Levine* and applied by the Ninth Circuit in *Gaeta v. Perrigo Pharm. Co.*—(1) did FDA give more than "passing attention" to the issue; (2) did FDA make or consider "an evaluation or analysis" of the issue; and (3) did FDA affirmatively "refuse to act" (i.e. change the labeling) in light of its evaluation or analysis. The answer to each question is a clear, "yes."

B. Plaintiffs' Four Points of Opposition Are Wrong.

Plaintiffs assert that defendants "begin with the exact argument rejected by *Levine*, ignore the CBE regulations, present no factual evidence *at all* relating to

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(Footnote Cont'd From Previous Page)

drug." 21 U.S.C. § 355(o)(4). Thus, FDA's approval of Tanzeum and Bydureon carry added significance, because FDA could have mandated a pancreatic-cancer warning had it believed the scientific evidence supported a causal association. The approval also has added significance because FDA acted in the face of "assertions concerning a causal association" between incretin-based therapies and pancreatic cancer. FDA/EMA Assessment at 796.

Even before FDA had authority to require labeling changes based on new safety information, however, the courts considered repeated approval of existing labeling as evidence supporting preemption. *Dobbs v. Wyeth Pharms.*, 797 F. Supp.2d 1264, 1273 (W.D. Okla. 2011) (citing as evidence supporting preemption that "FDA also approved more than a dozen [New and Supplemental Drug Applications] for other SSRI prescription drugs, and each approval required the same language").

labeling submissions or rejections, and then assert that continued FDA approval is itself proof that FDA would reject a labeling change." Opp. at 6. Plaintiffs are wrong on all counts.

First, far from quarreling with *Levine*, defendants' opening brief focused laser-like on *Levine's* test for preemption—Is there "clear evidence that the FDA would not have approved" a labeling change warning of the injury alleged by plaintiffs?[4] As almost every post-*Levine* court has commented, the Supreme Court did not say "what would amount to 'clear evidence.'"[5] Thus, plaintiffs ignore both *Levine* and its progeny when they assert that clear evidence can only consist of proof that FDA actually rejected "multiple proposed warnings and CBEs." No case so holds.[6]

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[4] Mem. of P. & A. at 1, 2, 11, 13, 15-20, 23.

[5] *Gaeta*, 630 F.3d at 1235 ("the only guidance this court has is that the evidence presented in *Levine* was insufficient to meet the clear evidence standard").

[6] The Opposition is careless in its citation of post-*Levine* authority. Under the heading, "Post-*Levine* Precedent Shows the Essential Element of Impossibility Is An Actual FDA Rejection For Safety Reasons," plaintiffs assert that "branded prescription drug manufacturers have been met with near universal rejection by the circuit courts" and cite four decisions. Opp. at 7 & n.16. *Desiano*, however, was decided *before Levine*. *Lefaivre* did not involve failure-to-warn claims and therefore did not even present the *Levine* question of whether FDA would have approved different labeling. Similarly, the preemption issue in *Wimbush* did not involve the plaintiff's failure-to-warn claims and did not apply *Levine*; indeed, the court affirmed summary judgment for the defendant on the failure-to-warn claims. Of the four cited Court of Appeals decisions, only *Mason* applied *Levine* to claims that the labeling was inadequate. But the facts in that case only serve to show, by contrast, why there is clear evidence here that FDA would not approve a pancreatic-cancer warning. In *Mason*, the evidence that FDA would not have approved a suicide warning for Paxil concerned (i) a different drug (Prozac), (ii) FDA actions taken "several years before [the plaintiff's] suicide," (iii) an FDA statement in a press release, not a peer-reviewed journal, and (iv) no mention that the FDA had conducted an independent study of the scientific evidence.

Indeed, as plaintiffs acknowledge, "'[A]pplication of the clear evidence standard is *necessarily fact specific*.'"[7] Such application focuses on FDA and its judgment at the relevant time whether the labeling adequately reflected the then-current scientific knowledge. Here, the evidence on that score is as clear, if not clearer, than in those post-*Levine* cases where the courts granted preemption motions, most notably the *Fosamax* MDL court. In *Glynn v. Merck, Sharp & Dohme Corp.*, 951 F. Supp. 2d 695 (D.N.J. 2013), Judge Pisano held that the plaintiff's claims were preempted because, only one month after the plaintiff's injury, FDA had rejected proposed labeling related to the same injury plaintiff alleged. The court so held despite the fact that the agency required the labeling change one year later, after further study. Thus, what mattered for purposes of preemption was FDA's clear declaration *at the relevant time* that the scientific evidence *at the time* did not warrant the proposed labeling change. Here, the agency's declaration is equally clear and even more emphatic: Within the last three months FDA has (i) issued an official statement in the *NEJM* that the labeling is adequate in light of the "current knowledge" about the specific risk of pancreatic cancer, (ii) responded to a Public Citizen Petition finding "no evidence that would support any changes to the current approved labeling," and (iii) approved two new incretin-based therapies without a pancreatic-cancer warning.

Second, far from ignoring the CBE regulation (never cited in the Opposition), defendants point to facts that show there is no valid basis under the regulation to submit a pancreatic-cancer warning. A manufacturer may act unilaterally to strengthen a warning only where "the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) . . . ." 21 C.F.R. §

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[7] *Id*. at 16 (quoting *Dobbs*, 797 F. Supp. 2d at 1270 (holding that plaintiff's claims were preempted) (emphasis added by plaintiffs)); *see also id.* at 1, 16 (calling the preemption defense "fact-intensive" and "fact specific").

314.70(c)(6)(iii). While the regulation does not require definitive proof of a causal relationship, 21 C.F.R. § 201.57(c)(6), it does require "reasonable evidence of a causal association." *Id*. In declaring officially that "assertions concerning a causal association" with pancreatic cancer are inconsistent with the scientific evidence and that the labeling adequately reflects that data, FDA necessarily determined that the evidence does not meet the CBE standard for "causal association." And, in denying the Public Citizen Petition, FDA underscored that determination. For plaintiffs to suggest that defendants could nevertheless add a pancreatic-cancer warning is to say that FDA would now disregard either its own regulations or its own findings. Under *Levine*, claims are preempted where FDA has "deemed … a warning inappropriate," 555 U.S. at 572, which is just what the agency has done four times in 2014.[8]

Third, plaintiffs are wrong that defendants "present no factual evidence" relating to labeling submissions and rejections. The notable omission is *plaintiffs' failure* to present evidence establishing that there is a material dispute of fact. It is undisputed that in 2014 FDA: (1) took the unprecedented step of publishing in the nation's most prestigious medical journal a public finding that the current labeling adequately reflects current scientific knowledge about the risks of incretin-based

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[8] Plaintiffs speculate that FDA would permit a pancreatic-cancer warning despite the absence of reasonable evidence of a causal association, because the current labeling includes a warning about pancreatitis (and, for Victoza, medullary thyroid cancer). But there is no basis for that speculation; the public record is plain in each instance what FDA *has done*. FDA considered the data regarding pancreatitis and concluded that, despite the lack of evidence of a causal relationship, a warning was appropriate. M. Parks & C. Rosebraugh, NEJM 2010;362:774-76, at 776. FDA likewise considered the safety data and decided to "address[] through labeling" concerns about a potential MTC risk. PCL at 13. Here, however, the public record clearly demonstrates a different, but equally definite, decision: After conducting a comprehensive review of the scientific data, FDA has concluded that a pancreatic-cancer warning *is not warranted*.

therapies; (2) rejected a petition to withdraw one such medication, finding no new evidence that "would support any changes to the current approved labeling"; and (3) twice approved new incretin-based therapies without requiring a pancreatic-cancer warning. Plaintiffs offer no contrary evidence, only the contrary assertion that FDA's ultimate conclusion that "'current knowledge is adequately reflected in the product information and labeling' relates *solely to pancreatitis*." Opp. at 12–13 (emphasis in original).

This is an erroneous, and truly desperate, assertion. The very first paragraph of the *NEJM* publication speaks of the agency's concern about postmarketing reports "of pancreatitis *and pancreatic cancer*." The statement explains that FDA and EMA "undertook comprehensive evaluations of a safety signal" involving both "pancreatitis *and pancreatic cancer*." It reports about FDA's re-evaluation of toxicology reports for purposes of identifying "*pancreatic tumors*"; its consideration of a pooled analysis of data from 25 clinical trials for evidence of "an increased risk of pancreatitis *or pancreatic cancer*"; and its discovery in two trials that the "reported incidence of *pancreatic cancer*" in the placebo group was double that in the medication group. It states, in summarizing the scientific evidence, that it does not support "assertions concerning a causal association between incretin-based drugs and pancreatitis *or pancreatic cancer*." And the agency explains its "[o]ngoing strategies" as including "the systematic capture of data on pancreatitis *and pancreatic cancer*." The notion, then, that FDA's conclusion relates solely to pancreatitis is nonsense.

Fourth, contrary to plaintiffs' assertion, defendants do not contend that mere "continued FDA approval" of the labeling is proof that the agency would reject a labeling change. Defendants rely, not on evidence of the FDA's inaction—in the form of passive, continued approval of the initial labeling—but unprecedented action in the form of a year-long, comprehensive evaluation of the scientific evidence culminating in (i) an official statement that the labeling is adequate with regard to

pancreatic cancer and (ii) rejection of a Public Citizen Petition to remove one of the medications from the market, finding no evidence regarding pancreatic-cancer risk "that would support *any* changes to the current approved labeling."[9]

C. **Plaintiffs Seek to Second-Guess FDA.**

A preemption motion is not exempt from Fed. R. Civ. P. 56. A plaintiff must still show that there are material facts in dispute. Here, plaintiffs concede that they "cannot currently present facts essential to justify their opposition to the Motion . . ." and seek time for extensive discovery hoping they might find some. Decl. of Michael K. Johnson, ¶ 4; Opp. at 1.[10] But the facts they seek to discover are not relevant to the issue here, namely, whether FDA would approve a pancreatic-cancer warning.

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[9] The *NEJM* statement's caveat that "FDA and the EMA have not reached a final conclusion at this time regarding such causal relationship" reflects nothing more than the truism that FDA's view may change if and when the scientific evidence changes. This commonplace caveat is no warrant for putting the summary judgment motion "on the shelf" based on plaintiffs' hope that new scientific evidence supporting their allegations will emerge in the fullness of time. "A trial court must function in the present assessing evidence that presently exists." *In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 615 (E.D. La. 2003).

[10] Plaintiffs speculate erroneously that there may be pancreatic-cancer events that certain defendants did not report, or improperly reported to FDA. Decl. of John M. Restaino, p. 2. In fact, all three pancreatic cancer cases that plaintiffs discuss were reported to FDA, which had the cases' information when it performed the analysis that resulted in February 2014 *NEJM* publication. Plaintiffs also reference issues in a pancreatic-cancer epidemiological analysis conducted in the i3 Aperio database. But as plaintiffs' own exhibits show, the original *and corrected* Aperio analyses were submitted to FDA in March 2011, long before the *NEJM* publication. And plaintiffs reference safety analyses, the final results of which were submitted to FDA. None of the documents that plaintiffs cite are relevant to this Motion, we submit, because the sole issue is whether FDA has focused on the question of a pancreatic-cancer risk and determined that no further warning is necessary. The evidence on that issue is clear. If, however, the Court has any questions about these documents (all of which have been produced), Defendants are prepared to address them.

Plaintiffs seek to prove that FDA's evaluation of the scientific evidence is wrong—that, as they allege, there are "multiple mechanisms by which Defendants' drugs may have the capacity to cause cancer," Opp. at 14—and plaintiffs complain that general causation discovery is not complete. But *Levine* does not authorize second-guessing FDA. The sole question is whether FDA would reject a pancreatic-cancer warning, not whether the soundness of that decision is scientifically debatable.

Plaintiffs try to fend off summary judgment on the hope or hunch that there is some information that a defendant should have submitted to FDA and that this information might have affected FDA's evaluation of the overall scientific data. But as the *Fosamax* MDL court held in granting summary judgment on preemption grounds, any evidence "relating to what [the manufacturer] *could have* or *should have* done, and what FDA *would have* done in response to the same, is pure speculation and does not rise to the level of being a genuine fact dispute."[11] There, it was a matter of fact that "FDA *did* reject" the labeling change, just as here it is a matter of undisputed fact that FDA has concluded four times in the last four months that a pancreatic-cancer warning is not warranted because a causal association between

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[11] *In re Fosamax Prods. Liab. Litig.*, 2014 U.S. Dist. LEXIS 42253, at *32 (D. N.J. Mar. 26, 2014) ("*Glynn II*"). The *Fosamax* court withheld decision on the preemption motion until it had completed the first MDL trial, and plaintiffs encourage this Court to do the same. But there is an important difference between the basis for preemption in *Glynn* and here. Regarding Fosamax, Merck's proof that FDA would not have approved plaintiffs' proposed labeling change consisted of regulatory communications over a period of years, and, therefore, the court understandably "wanted the parties to introduce *any and all relevant evidence*" from which an inference could be drawn before ruling. Here, in contrast, there is no need to piece together a regulatory record; FDA has taken the unprecedented step of publishing an official statement (i) finding that the scientific evidence is inconsistent with the assertion that incretin-based therapies cause pancreatic cancer and (ii) concluding that the labeling is adequate.

incretin-based therapies and pancreatic cancer is "inconsistent with the current data." In the end, plaintiffs stake their need for discovery on speculation. *If* the Court permits open-ended discovery, and *if* that discovery reveals that a defendant withheld information from FDA, and *if* that information was at all material to the question of causation, and *if* that information affected the overall weight of the evidence considered by FDA, then, they say, it is *possible* FDA might take a different view.

* * *

Any FDA labeling decision must be seen in the context of the agency's obligation to weigh evidence of risk against overall public health benefit.[12] As courts have recognized, a warning that is not based on reliable evidence of a causal relationship does not promote public health but rather will have the effect of limiting access to treatment. That is especially relevant for diabetes, a disease which has reached epidemic proportions and constitutes a major public health crisis.

FDA has recognized that incretin-based therapies are an important treatment option for patients with diabetes. Thus, when assertions were made in the scientific literature and the media about a possible causal association between the medications and pancreatic cancer, FDA acted in unprecedented fashion, launching its own comprehensive evaluation and reporting its findings, including its evaluation of the product labeling. FDA's well-considered conclusion—that a pancreatic-cancer warning is not warranted because a causal association is "inconsistent with the current data"—is *clear evidence* that FDA would not have approved such a warning.

[12] *See e.g.*, M. Parks & C. Rosebraugh, NEJM 2010;362:774-76, at 774.

Dated: May 27, 2014

Respectfully submitted,

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SIGNATURE ATTESTATION

Pursuant to Section 2.f.4 of the Court's CM/ECF Administrative Policies, I hereby certify that authorization for the filing of this document has been obtained from each of the other signatories shown above and that all signatories have authorized placement of their electronic signature on this document.

By: s/ Paul E. Boehm
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